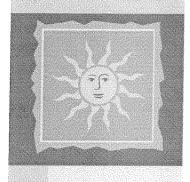
July/August 2002

Editor: Jean Eilertson, PharmD







PHARMACY SERVICE & THERAPEUTICS COMMITTEES

US ARMY MEDDAC, FORT CARSON, COLORADO

FORMULARY CHANGES

The Pikes Peak Region Formulary Committee met on 27 June 2002 and the Evans Pharmacy & Therapeutics (P&T) Committee met on 9 July 2002 with the following medications **added** to the Formulary:

- + amoxicillin / clavulanic acid (*Augmentin ES*) 600mg/5ml suspension once reconstitued, total volume 150ml
- + ethinyl estradiol 5mcg / norethindrone acetate 1mg, 28 tablet blister card (*Femhrt*) added to Formulary due to problems procuring *Prempro*

No medications were **deleted** from the Formulary.

The Pikes Peak Region Formulary Committee reviewed the cardiovascular agents - no changes were made to the Formulary. As part of this ongoing drug class review process, the Committee (with representatives from the Air Force Academy, Peterson AFB, and Evans) will conduct reviews as follows:

September 2002 = endocrine/hematologic agents

November 2002 = gastrointestinal/renal/genitourinary agents

January 2003 = central nervous system agents

March 2003 = dermatologic/ophthalmologic agents

Pharmaceuticals submitted for Formulary consideration will be reviewed based on the above schedule. If a medication is a new entity, it may be considered earlier if submitted via a New Drug Request. Providers desiring to have input into the drug class reviews are encouraged to contact one of the Pikes Peak Committee members: LTC Edward Torkilson (Pharmacy), MAJ Robert Gray (Family Practice), and Dr. Garold Paul (Internal Medicine).

The next Formulary Committee Meetings will be held on Thursday, 5 September (Pikes Peak), and Tuesday, 10 September (Evans' P&T). New Drug Requests must be received by the Chief, Pharmacy Service, no later than **23 August** to be considered at the next meetings.

WEBSITES OF INTEREST

evans.amedd.army.mil – Evans' homepage
evans.amedd.army.mil/pharmnew/default.htm — Evans' pharmacy website
www.pec.ha.osd.mil – DoD Pharmacoeconomic Center, Ft Sam Houston
www.cs.amedd.army.mil/qmo/pguide.htm – DoD/VHA Practice Guidelines; recently added
guidelines include Ischemic Heart Disease, Chronic Heart Failure, Kidney Disease,
Uncomplicated Pregnancy, Health Promotion and Disease, Prevention Indicators (Adults),
Substance Abuse Disorder, Medically Unexplained Symptoms — Chronic Pain and Fatigue

Vaccine & Immunization Websites

www.immunofacts.com/statistical.html — ImmunoFacts, run by LTC (Dr.) John Grabenstein www.cdc.gov/nip/ — Centers for Disease Control and Prevention; contains information on current vaccine delays and shortages

www.cdc.gov/nip/ACIP/default.htm — Advisory Committee on Immunization Practices www.anthrax.osd.mil — DoD Anthrax Vaccine Immunization Program www.cdc.gov/travel/ — National Center for Infectious Diseases Travelers' Health

0 & A

What are the recommended doses for the COX2 Inhibitors (celecoxib and rofecoxib) at Evans (based on the current guidelines for use) and what did a recent review show regarding compliance with these guidelines?

see page 6

In this issue....

- > Formulary Committee News
- ➤ New Guidelines
- ➤ Niaspan in Diabetes
- ➤ In the News...
- ➤ Recent FDA Approvals
- ➤ Herb (Comfrey)
- ➤ ADR Report
- ➤ MUR Report

NEW GUIDELINES PUBLISHED

The National Asthma Education and Prevention Program (NAEPP) has issued an update on selected topics in the Guidelines for the Diagnosis and Management of Asthma. The guidelines now recommend inhaled corticosteroids as safe, effective and



preferred first-line therapy for children as well as adults with persistent asthma. The update also includes considerations on when to start asthma control therapy in infants and children under age 5; new recommendations regarding the use of leukotriene modifiers as alternative therapy for treating mild persistent asthma or as combination therapy in moderate asthma; reaffirmation that antibiotics should not be used to treat acute asthma attacks except when a bacterial infection due to another condition is present (such as pneumonia or sinusitis); and a review of benefits of written action plans for self-management. The Executive Summary can be found at:

www.nhlbi.nih.gov/guidelines/asthma/index.htm

The American Heart Association published their AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update in the July issue of Circulation. Update recommendations: begin risk factor assessment in adults at age 20; update family history of CHD regularly; assess diet, physical activity, tobacco use, and alcohol intake at

every routine evaluation; record BP, BMI, waist circumference, and pulse (to screen for atrial fibrillation) at each visit (at least every 2 years); and measure fasting serum lipoprotein profile (or total cholesterol and HDL if fasting unavailable) and fasting blood glucose according to the person's risk for hyperlipidemia and diabetes (at least every 5 years; every 2 years if risk factors present). Additional recommendations include:

- ◆ BP goal of <140/90; <130/85 if renal insufficiency or heart failure; <130/80 if diabetes
- ◆ Low-dose aspirin (75mg to 160mg per day) recommended for those at higher risk of CHD
- ◆ BMI of 18.5 to 24.9; if BMI ≥ 25kg/m², waist measurement goal of ≤ 40 inches for men and ≤ 35 inches for women

For additional recommendations (lipid profile, fasting glucose, exercise), see: circ.ahajournals.org/cgi/content/full/106/3/388

The Committee on Atherosclerosis, Hypertension, and Obesity of the Council on Cardiovascular Disease in the Young of the American Heart Association has published new guidelines to promote cardiovascular health among US children, published in the July issue of *Circulation*. The guidelines focus on several areas including screening for hypertension and high cholesterol, preventing obesity, and promoting physical activity and nonsmoking. The guidelines can be found at:

circ.ahajournals.org/cgi/content/full/106/1/143



New guidelines for neonatal neuroimaging from the American Academy of Neurology and the Child Neurology Society have been published in the June issue of *Neurology*. The guidelines, endorsed by the American Academy of Pediatrics, the American Society of Pediatric Neuroradiology, and the Society for Pediatric Radiology, can be found at:

www.aan.com/professionals/practice/guidelines.cfm

NIASPAN USE IN DIABETIC PATIENTS

The results of the ADVENT (Assessment of Diabetes Control and Evaluation of the Efficacy of *Niaspan* Trial) study was published in the July issue of *Archives of Internal Medicine*. The study was a 16-week, double-blind, placebo-controlled trial with 148 patients randomly assigned to either placebo (n=49), 1,000mg/day *Niaspan* (n=45), or 1,500mg/day *Niaspan* (n=52). The authors concluded that low doses of *Niaspan* (extended-release niacin) alone or in combination with a statin (47% of patients concomitantly on a statin) significantly improved lipid profiles in patients with type 2 diabetes with a minimal impact on blood



sugar control. In the study, *Niaspan* increased HDL levels by as much as 24% and reduced triglyceride levels by as much as 36%. At 16 weeks, patients receiving 1,000mg/day or 1,500mg/day of *Niaspan* showed no statistically significant increase in fasting blood glucose compared to placebo (note: 4 patients discontinued enrollment in the study due to inadequate glucose control). HbA1c levels were unchanged compared with placebo in patients receiving 1,000mg/day and increased 0.03% in patients receiving 1,500mg/day (p=0.048). No patient experienced elevated liver enzymes greater than three times the upper limit of the reference range, and there were no reports of drug-induced myopathy even among patients concomitantly on a statin (mostly *Lipitor*).

"All that's different about me is that I still ask the questions most people stopped asking at age five." ~ Albert Einstein

JULY/AUGUST 2002

IN THE LITERATURE...

According to the results of the Women's Pooling Project (a prospective cohort study combining data from 8 longitudinal studies involving 24,343 ethnically diverse women), high cholesterol is a significant risk factor for nonhemorrhagic stroke-related death in relatively young women without a history of cardiovascular disease. Published in the July issue of *Stroke*, the study evaluated the risk of death caused by different types of stroke by race, age, and cholesterol level. The investigators reported that 568 women died a stroke-related death (461 nonhemorrhagic and 83 hemorrhagic) during 339,215 person-years of follow-up. A positive continuous relationship between rising cholesterol levels and increased risk of death from nonhemorrhagic stroke in women younger than 55 at baseline emerged; each 1mmol/L increase in cholesterol was associated with a 23% increased risk of nonhemorrhagic stroke death. African American women had a significantly greater risk of dying from a stroke than white women.

In Archives of Internal Medicine, investigators from the VA Healthcare System and Brigham and Women's Hospital evaluated both intensive and passive education methods and found both seemed to work equally well in improving glycemic control in patients with elevated HbA1c levels. Intensive-education participants (3.5 days of structured curriculum taught by five staff including a physician, a nurse, a pharmacist, an exercise physiologist, and a social worker) had a decrease of 2% in HbA1c in 12 months compared to a decrease of 1.9% in passive-education participants (received basic diabetes information by mail every 3 months). The authors suggested those who enrolled in the study were highly motivated and prepared to make changes in their diabetic control so they compared the outcomes in both groups to those who refused to participate in the study – those who declined also had a decrease in HbA1c but it was significantly less than the intervention groups. The authors concluded that the results reinforce the need for and benefits of incorporating educational interventions into the management of diabetic patients.

A study published in the July issue of *Diabetes Care* suggests that women with type 2 diabetes are at substantially elevated risk of morbidity and mortality from cardiovascular disease even before their diabetes is diagnosed. The investigators followed 117,629 female nurses (baseline age 30 to 55 years and free of diagnosed cardiovascular disease) for 20 years. During 2.2 million person-years of follow-up, the investigators documented 1,556 new cases of MI, 815 cases of fatal CHD, 1,405 strokes, and 300 fatal strokes. Among women who developed type 2 diabetes during the follow-up period, the age-adjusted relative risks of MI were 3.75 for the period before the diagnosis and 4.57 after diagnosis, compared with women who had remained free of diabetes. When adjusted for BMI, smoking, and other cardiovascular risk factors, the multivariate relative risks were 3.17 and 3.97. The risk of stroke was also significantly elevated before diagnosis of diabetes (multivariate relative risk of 2.30).

A study done at the University of Southern California Keck School of Medicine and USC/Norris Comprehensive Cancer Center found that cases of breast cancer among Asian American women have been increasing rapidly. The study, published in the June issue of the *International Journal of Cancer*, is based on cancer cases reported in the mid-to-late 1990s to the Los Angeles Cancer Surveillance Program. The authors state that since Los Angeles County is an ethnically diverse county, breast cancer rates in the county are similar to the rate nationwide. Among Asian women 50 years or older, diagnosed cases increased about 6.3% a year during the five-year period of 1993 to 1997 versus an increase of 1.5% in non-Hispanic white women 50 years or older during the same time period. The authors also stated that the breast cancer incidence for Japanese American women in Los Angeles County is the highest reported anywhere in the world and that in Japan studies have shown that the incidence also has increased dramatically (more than doubling from 1960 to the late 1980s).

RECENT FDA APPROVALS

Orphan Medical, Inc...for *Xyrem* (gamma hydroxybutyrate) for patients with cataplexy associated with narcolepsy. Use will be tightly controlled (will be a controlled substance) as the drug was banned in the 1990s due to its use in date rapes. Dispensing will be through a single, centralized pharmacy.

Pfizer...to market Neurontin (gabapentin) for the management of post-herpetic neuralgia (PHN).

Schering-Plough...to expand the indication of *Nasonex* (mometasone furoate) for the treatment of seasonal and perennial nasal allergy symptoms to include children 2 years of age and older.

Novartis...for *Ritalin LA* (methylphenidate HCl) extended-release capsules for the treatment of ADHD. Available as 20mg, 30mg, and 40mg beaded capsules, it may be swallowed whole or administered by sprinkling the contents of the capsule on applesauce.

GlaxoSmithKline...for re-marketing of *Lotronex* (alosetron) for use in women with severe diarrhea-predominant irritable bowel syndrome who have failed to respond to conventional therapy whose IBS symptoms are chronic and who have had other GI medical conditions that could explain their symptoms ruled out. *Lotronex* was voluntarily withdrawn by the manufacturer in November 2000.

Pfizer...for Geodon Injection (ziprasidone mesylate — IM administration) for the rapid control of agitated behavior and psychotic symptoms such as hallucinations and delusions in patients with acute exacerbations of schizophrenia.



Drug Interaction Corner

Medications that can increase the risk for statin-associated myopathy:

- ⇒ Fibrates (especially gemfibrozil, but other fibrates too)
- ⇒ Nicotinic acid (rarely)
- ⇒ Cyclosporine

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- ⇒ Azole antifungals
- ⇒ Itraconazole and ketoconazole
- ⇒ Macrolide antibiotics
- ⇒ Erythromycin and clarithromycin

- ⇒ HIV protease inhibitors
- ⇒ Nefazodone (antidepressant)
- ⇒ Verapamil
- ⇒ Amiodarone
- ⇒ Large quantities of grapefruit juice (usually more than 1 quart per day)

⇒ Alcohol abuse (independently predisposes to myopathy)

For the ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins (with information on CK monitoring) see: www.acc.org or www.americanheart.org or www.nhlbi.nih.gov/guidelines/cholesterol

Thanks Dr. Paul for this reference!

ADVERSE DRUG REACTION REPORT

There were 36 adverse drug reactions (ADRs) documented for May (n=16) and June (n=20), of which 22 (61%) were reported **spontaneously** (5 from Internal Medicine; 4 each from PACC and pharmacy; 2 each from Family Practice, Pediatrics, and Preventive Medicine; and 1 each from Emergency Department, Recovery Room, and 5E). The most prevalent adverse events reported involved the anti-infective agents (n=14; 39%) and the psychotherapeutic agents (n=6; 17%). The anti-infective agents continue to be the top medication class involved in reported adverse events with dermatologic manifestations of the adverse events the top system involved.



One event was deemed moderate in severity which involved a 19 year old male who was prescribed *Celexa* 40mg 1/2 tab daily and naltrexone 50mg daily (patient with dysthymia and alcohol dependence) who took both medications as directed and within a few hours vomited, became poorly responsive, and grossly tremulous (tremors have been reported with *Celexa*, somnolence/dysphoria reported with naltrexone). The patient was brought to the Emergency Department and admitted. The symptoms resolved; patient was seen by Psychiatry and discharged the next day with follow-up in Mental Health.

No events were deemed preventable. Five events were reported from inpatient areas: 1 resulting in admission (case above), 1 noted on admission (not primary diagnosis for admission; 76yo male with elevated INR without s/sx of overanticoagulation), and 3 occurring during hospitalization (6yo male with vomiting secondary to IV erythromycin, 52yo female with itching secondary to IV morphine, and a 29yo female with itching/hives on face and forehead secondary to IV ketorolac).

Thanks to all who continue to report adverse drug events.

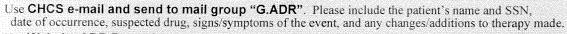
EVANS' ADR DEFINITION

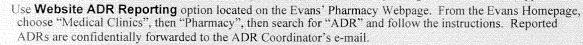
An adverse drug reaction (ADR) is any **unwanted or unintended effect** of a drug following prescribed doses that (1) requires some sort of management including, but not limited to, discontinuation of the causative medication or treatment with another drug; (2) adversely impacts the outcome or progress of the patient's clinical condition; or (3) results in death, hospitalization, prolongation of hospital stay, transfer to a more intense level of care, or significant discomfort/distress to the patient.

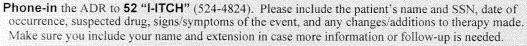


HOW TO REPORT AN ADR

Complete the **Adverse Drug Reaction Reporting Form** and forward to the pharmacy. For forms, call the pharmacy at 526-7334.







Phone-in the ADR to the Inpatient Pharmacy at 524-4400 from 0600 to 2300 or call 526-7334 and leave a voice mail message with the information listed above. Make sure you include your name and extension in case more information or follow-up is needed.





From the 62nd Scientific Sessions of the American Diabetes Association...

- Diabetic patients have a high rate of potentially avoidable vision loss and blinding eye conditions ... data from the 1999 National Health Interview Survey on self-reported blindness, visual impairment, cataract, glaucoma, and macular degeneration and the 2000 Behavioral Risk Factor Surveillance System on self-reported diabetic retinopathy was reviewed by Dr. Daaddine from the CDC ... results showed that people with self-reported diabetes were more likely to have blindness than people without diabetes (1.4% vs 0.6%), severe visual impairment (12.6% vs 4.6%), cataract (26.4% vs 14.9%), glaucoma (6.9% vs 3.6%), and macular degeneration (3.6% vs 2.2%) ... 25% of diabetics reported having diabetic retinopathy ... among people with diabetes, age was highly related to all visual problems
- Adult Treatment Panel (ATP III) Guidelines inadequate for identifying metabolic syndrome ... investigators from Cook Children's Medical Center, Fort Worth, TX analyzed NHANES III to estimate the number of US adults who meet criteria for metabolic syndrome (having three or more of the markers defined by ATP III: abdominal obesity defined as waist circumference > 102 cm in men and 88 cm in women, triglycerides ≥ 150mg/dL, HDL < 40mg/dL in men and < 50mg/dL in women, BP ≥ 130/85, fasting glucose ≥ 110mg/dL) and to estimate the number of adults who would be recommended for lipid-modifying therapy ... an estimated 23% of US adults have the metabolic syndrome ... based on ATP III, only 39% of those identified with metabolic syndrome would be recommended for drug therapy ... investigators stated in those with

NEW ... MAJ Shaw. FNP, is now providing a Weight Management Clinic through the DMC and may prescribe Xenical to patients enrolled. To refer a patient, enter a consult to "DMC-Card Risk Factors" and indicate enrollment to the weight management program.

metabolic syndrome and triglycerides \geq 200mg/dL, non-HDL cholesterol should be an important secondary target in ATP III ... they concluded: "clinical trial data is needed to determine whether pharmacological therapy for dyslipidemia is indicated in these patients and whether the focus should be solely on reductions in LDL or on comprehensive improvements to the lipid profile"

- Xenical (orlistat) helpful for type 2 diabetics with high HbA1c levels ... investigators at the U of TX Southwestern Medical School, Dallas, presented data on a pooled analysis of 7 multicenter, double-blind trials evaluated to study the effect of adjunctive orlistat treatment on glycemic control in overweight or obese patients (BMI 28 to 43) with type 2 diabetes who also had a baseline HbA1c of ≥8% ... patients were randomized to orlistat 120mg/day or placebo in addition to a mildly reduced caloric diet and metformin, sulfonylurea, and/or insulin ongoing for no more than 1 year ... mean baseline HbA1c approximately 9.3% ... a significantly (p<0.0001) greater decrease in HbA1c was seen in the 728 patients treated with orlistat than in the 699 treated with placebo ... a significantly (p<0.0001) higher proportion of orlistat-treated patients showed a decrease of at least 0.5% (63.9% orlistat vs 46.9% placebo) or at least 1% (49% orlistat vs. 33.5% placebo) in HbA1c
- Orlistat found beneficial in type 2 diabetes with differing HbA1c levels ... Dr. Ralph DeFronzo from the U of TX Health Science Center, San Antonio, presented data from 7 multicenter, double-blind trials with 1,230 placebo group patients and 1,249 orlistat-treated group patients ... results showed weight loss from baseline was significantly greater for those treated with orlistat than those in placebo group (-3.8% vs 1.4%) ... orlistat-treated patients had a significantly larger decrease in HbA1c than placebo patients (-0.7% vs -0.3%) ... in all subgroups with differing baseline HbA1c levels, those treated with orlistat had a greater reduction in HbA1c from baseline to end point than those on placebo

HERB OF THE (every other) MONTH



Comfrey (also known as blackwort, bruisewort, knitbone, slippery root) is a perennial herb that grows in temperate regions including western Asia, North America, and Australia in moist meadows and along creeks and streams. The whitish or pale purple flowers have a tubular corolla resembling the finger of a glove and bloom from May to August. The roots and leaves are used in herbal preparations. Historically, comfrey was used for several internal ailments such as ulcers of the bowel, stomach, liver, and gallbladder. It has also been used to heal damaged bones, hence the name "knitbone". However, because the alkaloids are converted to toxic metabolites by liver enzymes after ingestion, internal use is no longer recommended.

Preparations are made from *Symphytum officinale* and are available as a tea (dried leaf and whole root), blended plant extract ("green drink"), and a cream. It contains a few compounds that show medicinal activity. Mucilage, a mucopolysaccharide of fructose and glucose, is concentrated in the root up to 29%. Allantoin, tannin, pyrrolizidine alkaloids, triterpenoids, asparagines, and a phenolic acid are also found in the plant. The mucilage is reported to possess demulcent properties by forming a protective film, soothing irritation and inflammation; allantoin is claimed to be a cell-growth stimulator; tannin provides astringent properties; and rosmarinic acid (a phenolic acid) possesses anti-inflammatory properties.

Comfrey contains pyrrolizidine alkaloids toxic to the liver and studies in animals suggest it is carcinogenic. It has been banned in Canada and is severely restricted in Germany. The root and leaves are approved for use in Germany by the Commission E for external use only for bruises, pulled muscles and ligaments, and sprains. The herb is applied as an ointment or other preparation for external application with 5% to 20% dried drug and applied ONLY to intact skin for a limited duration of 10 or less days.

Adverse effects include its carcinogenic potential (hepatocelluar adenomas and urinary bladder tumors seen in animals) and hepatotoxicity (hepatic venoocclusive disease caused by pyrrolizidine alkaloids). It is contraindicated for internal use, in pregnant or breastfeeding patients, and in young children. No interactions with oral medications are known for topical preparations.

Resources: Complementary & Alternative Medicines (1999), The Review of Natural Products (1995), Various Websites

MUR COMMITTEE REPORT, RHONDA EUSTICE, PHARMD

COX2 Inhibitor Use - Provider Profiles

Purpose:

- ♦ The lowest effective dose of Celebrex and Vioxx should be sought for each patient
- * A preliminary CHCS review of COX2 inhibitor use indicated that many patients are being given high dose *Celebrex* or *Vioxx* initially and kept on these doses

Q & A Note: indication of these dosing guidelines are listed as a prompt in CHCS when you order the medication

Evans' Guidelines for the use of COX2 inhibitors:

- 1) Based on manufacturer recommendations:
 - Celebrex: OA in adults = 200mg daily as a single dose or as 100mg twice daily RA in adults = 100mg to 200mg twice daily
 - Vioxx: OA in adults = 12.5mg to 25mg daily
- 2) Prescriptions for *Celebrex* 200mg twice daily or *Vioxx* 50mg daily will only be for patients with documented rheumatoid arthritis (RA) or ankylosing spondilitis no other conditions are indicated for these doses
- 3) Vioxx 25mg or 50mg may be written for **SHORT-TERM** therapy (not to exceed 10 days with no refills) prior to and immediately after surgical procedures
- 4) COX2 inhibitors are no more effective than conventional NSAIDs

Documented Diagnosis: 95 medical records reviewed

- ♦ chronic pain 52%

Findings:

- ♦ 64% of high dose Celebrex and Vioxx prescriptions were started by EACH providers
- ♦ Downward dose titration was attempted in 13% of patients
- ♦ 45% of patients were started and kept on the same high dose of Celebrex or Vioxx
- ♦ 33% of patients were started on the manufacturers' recommended dose and increased
- 3% of patients were on the manufacturers' recommended dose and when renewed, a higher dose was given with no mention of dose increase in the medical record
- ♦ COX2 inhibitors are not indicated for acute pain except for pre- and post-surgery (Vioxx): 41% of prescriptions were given for acute pain
- ♦ COX2 inhibitors can increase blood pressure in some patients
- ♦ The lowest effective dose of Celebrex and Vioxx should be sought for each patient to minimize adverse effects and to contain costs

MUR Committee Recommendations:

- 1) Attempt titrating high dose COX2 inhibitors to lowest effective dose
- 2) If Celebrex 200mg daily or Vioxx 25mg daily is not effective for OA, consider switching patient to another agent
- 3) Do not use these agents for acute pain unless for pre-/post-surgery
- 4) Monitor for adverse effects: watch BP for patients receiving COX2 inhibitors; GI side effects are not as prevalent with these agents compared to the conventional NSAIDs, but they have the same (possibly more) renal effects



Hypertension Review — July 2002

Purpose:

* A retrospective review was performed to determine if initial elevated blood pressures are being rechecked at patient appointments, and if high blood pressure readings are being addressed.

Results: 113 medical records reviewed

- 44% of high initial blood pressure readings are not being rechecked
- \$\delta\$ 24% of patients had an ICD-9 code for hypertension (401.9) when hypertension was not addressed in the clinic note by
 the provider

MUR Committee Recommendations:

- 1) Recheck elevated BP readings
- 2) Only code for hypertension if there is documentation of assessment. If hypertension is only part of the patient's past medical history and is not addressed at the appointment, it should not be coded for.